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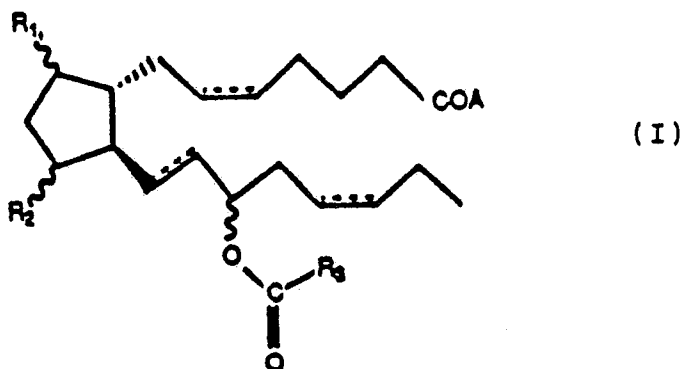
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Intraocular pressure reducing 15-acyl prostaglandins.

The invention provides ophthalmic compositions for reducing ocular hypertension comprising an ophthalmically acceptable excipient and at least one compound of the formula:



wherein the dotted lines represent a single bond, or a double bond in the cis or trans configuration; A is OH or a pharmaceutically acceptable salt thereof or OR₅; R₁ and R₂ combined are -OH/-OH, =O/-OH, or -OH/=O; R₃ is an acyclic hydrocarbon, saturated or unsaturated, having from 1 to 20 carbon atoms, or R₃ is -(CH₂)_nR₄ where n is 0-10; R₄ is an aliphatic ring from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R₅ is an aliphatic radical of from 1 to 10 carbon atoms.

Also provided are novel 15-acyl prostaglandins and a process for the preparation of 15-acyl prostaglandins.

EP 0 399 839 A2

INTRAOCULAR PRESSURE REDUCING 15-ACYL PROSTAGLANDINS

The present invention relates to a means for reducing or maintaining intraocular pressure. More particularly it relates to a method and composition for reducing or maintaining intraocular pressure involving the administration of a composition containing a 15-acyl prostaglandin in an ophthalmically acceptable carrier.

5 The method and compositions of the present invention are particularly useful for the management of glaucoma, a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults, congenital glaucoma, may be either chronic open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged
10 cataract.

The underlying causes of primary glaucoma are not yet well known. The increased intraocular tension is due to obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute and chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed and the iris may
15 obstruct the trabecular meshwork at the entrance to the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle or may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of varying degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior
20 chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

25 Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptomatic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β -adrenoceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and C-1 esters of certain prostaglandins, have been reported to possess ocular
30 hypotensive activity. However, prostaglandin ocular hypotensives generally suffer from the disadvantage of inducing conjunctival hyperemia of varying severity and duration, smarting, and foreign body sensation, as well as presenting solubility problems in certain ophthalmically advantageous carriers.

This invention relates to derivatives of the known prostaglandins formulated in a pharmaceutically acceptable vehicle, and ophthalmic use of those prostaglandins. The present invention has numerous
35 advantages over the prior art, including increasing duration of action or reduction of the aforementioned undesirable side effects, along with being easily solubilized in certain ophthalmically advantageous carriers.

Summary of the Invention

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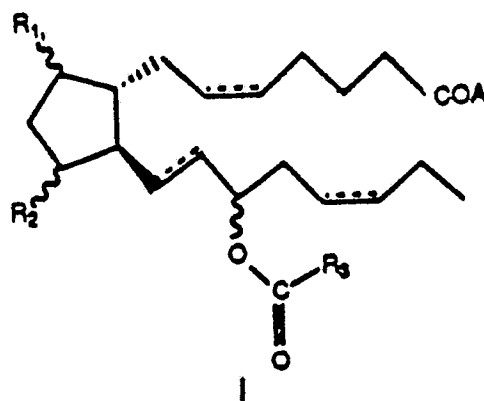
In accordance with one aspect of the present invention, there is provided an ophthalmically acceptable composition for reducing ocular hypertension which comprises an ophthalmically acceptable excipient and at least one compound of the formula (1):

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15 wherein the dashed bond represents a single or double bond which can be in the cis or trans configuration; A is -OH, or a pharmaceutically acceptable salt thereof or -OR₅; R₁, R₂ is -OH, -OH, =O, -OH, or -OH, =O; R₃ is an acyclic hydrocarbon, saturated or unsaturated, having from 1 to 20 carbon atoms, or R₃ is -(CH₂)_nR₄ where n is 0-10 and R₄ is an aliphatic ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring, preferably of 5 or 6 carbon atoms; and R₅ is an aliphatic radical of from 1 to 10 carbon atoms.

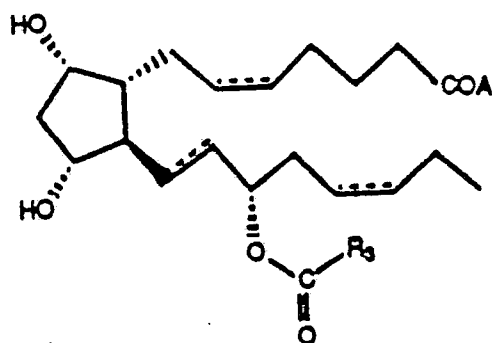
20 The ophthalmically acceptable excipient is one which does not have a deleterious or untoward effect on the eye when used in normal treatment regimens.

Certain of these 15-acyl prostaglandins are novel chemical entities, and thus, in a further aspect, the present invention provides a compound of the formula (1a):

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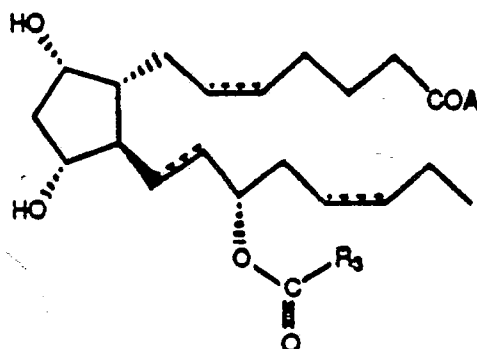
(1a)

wherein the dotted lines represent a single bond or a double bond in the cis or trans configuration; A is -OH or a pharmaceutically acceptable salt thereof or OR₅; R₃ is an acyclic hydrocarbon, saturated or unsaturated, having from 4 to 20 carbon atoms (eg. 5 or more carbon atoms), or R₃ is -(CH₂)_nR₄ where n is 0-10; R₄ is an aliphatic ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R₅ is an aliphatic radical of from 1 to 10 carbon atoms.

45 In a still further aspect, the present invention provides a method for the preparation of a compound of the formula (1b) by esterifying the corresponding compound containing a 15-hydroxyl group, wherein said compound of the formula (1b) has the structure shown below:

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(1b)

wherein the dashed bond represents a single bond or a double bond which can be in the cis or trans configuration; A is OH or -OR₅; R₃ is an acyclic hydrocarbon, saturated or unsaturated, having from 1 to 20 carbon atoms, or R₃ is -(CH₂)_nR₄ where n is 0-10; R₄ is a hydrocarbon ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R₅ is an aliphatic radical of from 1 to 10 carbon atoms; which

5 method comprises:

(a) esterifying the C-1 acid function;

(b) treating the resulting C-1 ester with an alkyl-boronic acid in an inert solvent at a temperature up to reflux for up to 2 hours to effect formation of a 9,11-cyclic-boronate, C-1 ester;

(c) treating the boronate compound, with or without a basic solvent with 4-dimethylaminopyridine and
10 an acylating agent, eg. an acid anhydride or an acyl halide at ambient temperature or above for a time sufficient to effect esterification of the C-15 hydroxyl group;

(d) hydrolyzing the 9,11-cyclic-boronate ester; and, when it is required to prepare a compound wherein R₅ is OH;

(e) saponifying the C-1 ester.

15 Particular and preferred aspects of the invention are as defined in the appended claims. Further features and advantages of the present invention will become apparent from the detailed description of preferred embodiments which follows, taken together with the examples and claims appended hereto.

20 Detailed Description of Preferred Embodiments

It has been discovered that certain prostaglandins lower intraocular pressure in man and other mammals when applied topically to the eye. Although the precise mechanism is not yet known, prostaglan-
25 dins appear to increase aqueous humor outflow to restore a normotensive or hypotensive state. However, topical application of prostaglandins generally causes side effects such as conjunctival hyperemia, smarting and foreign body sensations which range in degree from undesirable to unacceptable, depending upon the particular patient and dosage necessary to produce a sufficient pressure regulating effect.

In accordance with the present invention, it has been discovered that the esters of formula 1, are more
30 effective than PGF_{2α} both in terms of degree and duration of activity. In addition, animals treated with formulations comprising these esters experience reduced adverse side effects, notably ocular surface hyperemia.

In the foregoing illustration, as well as those provided hereinafter, wavy line attachments indicate either the alpha (α) or beta (β) configuration. The dotted lines on bonds between carbons 5 and 6 (C-5), between
35 carbons 13 and 14 (C-13), and between carbons 17 and 18 (C-7) indicate a single or double bond which can be in the cis or trans configuration. If two solid lines are used at C-5, C-13, or C-17, that indicates a specific configuration for that double bond. Hatched lines used at positions C-9, C-11 and C-15 indicate the α configuration. If one were to draw the β configuration, a solid triangular line would be used at either of these three positions.

40 The naturally occurring stereochemistry of PGF_{2α} includes the C-9, C-11 and C-15 hydroxyl groups in the α configuration. In the compositions of the present invention, however, esters of prostaglandins having the C-9 or C-11 or C-15 hydroxyl group in the β configuration are also contemplated. In addition to configurational variations, the substituent group at each of the 9 and 11 positions may be varied. Designating the C-9 substituent as R₁, and the C-11 substituent as R₂, 15-acyl prostaglandins for use in the
45 method of the present invention may be substituted such that R₁ and R₂ taken together in that order are -OH/-OH, =O/-OH, or -OH/=O.

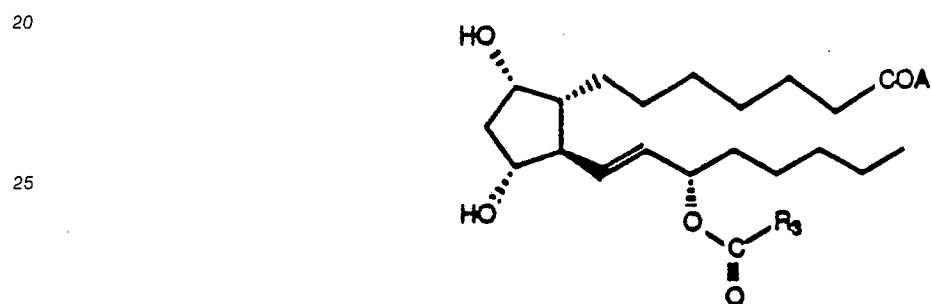
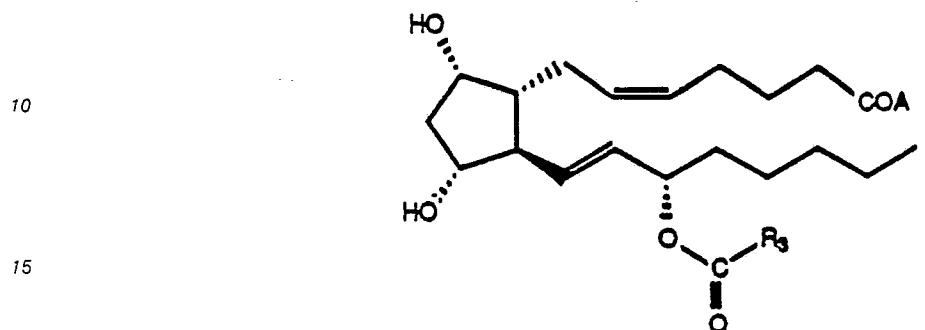
The 15-acyl prostaglandins suitable for use in this invention can comprise any of a variety of acyl substituents at the 15 position. As per the formulae, R₃ can be an aliphatic acyclic hydrocarbon having from one to twenty carbon atoms, inclusive. Preferably R₃ has from one to ten carbon atoms. More preferably R₃
50 is methyl, ethyl, propyl, butyl, pentyl, or an isomeric form thereof. The preferred isomeric forms are the isopropyl, n-butyl, isobutyl or t-butyl isomers.

Alternatively R₃ can comprise a cyclic component. In particular, R₃ can be (CH₂)_nR₄ where n is 0-10 and R₄ is a saturated or unsaturated ring, preferably a saturated ring having from three to seven carbon atoms, inclusive, or an aromatic or heteroaromatic ring of 5 to 7 carbon atoms, and having oxygen, nitrogen
55 or sulfur in the case of a heteroaromatic ring. Preferably n is 0-4.

In all formulations provided herein broken line attachments to the cyclopentane ring indicate substituents in the α configuration. Thickened solid line attachments to the cyclopentane ring indicate substituents in the β configuration. For instance, 9β-PGF compounds have the same structure as the above

PGF_α compounds, except that the hydroxyl at the C-9 position is in the β configuraion. Also, the broken line attachment of the hydroxyl group to the C-15 carbon atom signifies the α configuration; therefore, compounds with the epi configuration for the hydroxyl group at C-15 are designated by using 15β and if there is no indication of the β configuration, the configuration is assumed to be α.

5 The preferred compounds of this invention are those which have the following structures.



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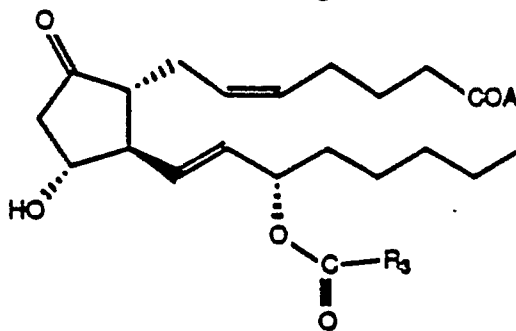
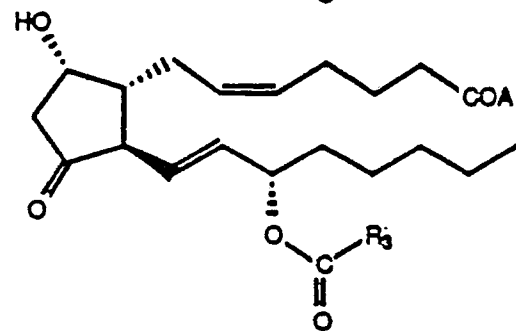
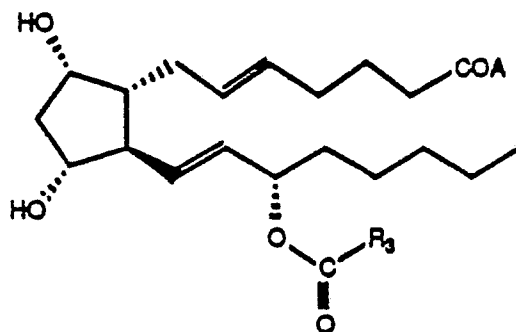
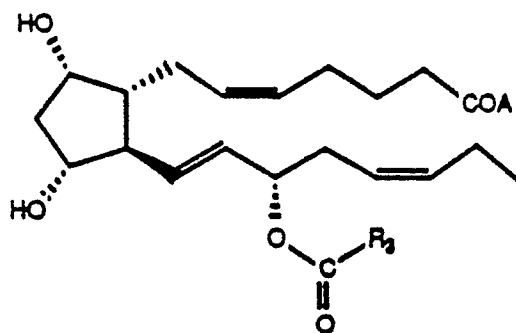
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Within this preferred group, the most preferred compounds are those where R_3 is $-\text{CH}(\text{CH}_3)_2-(\text{CH}_2)-$
 $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ or $-\text{C}(\text{CH}_3)_3$.

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Where A is $-\text{OH}$ the acid can be converted to a salt O^-X^+ where X^+ is the anion component of any of a
 variety of pharmaceutically acceptable salts. A pharmaceutically acceptable salt may be prepared for any
 compound in this disclosure having a functionality capable of forming such salt, in particular, the carboxylic
 acid group at C_1 of the prostaglandins disclosed herein. A pharmaceutically acceptable salt is any salt
 which retains the activity of the parent compound and does not impart any deleterious or undesirable effect
 on the subject to which it is administered and in the context in which it is administered.

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A pharmaceutically acceptable salt of an acid may be derived from an organic or inorganic base. Such
 salt may be a mono- or polyvalent ion. Of particular interest are the inorganic ions, sodium, potassium,
 calcium, magnesium, and zinc. Organic ammonium salts may be made with amines, such as mono-, di-,
 and trialkyl amines or ethanolamines. Salts may also be formed with caffeine, tromethamine and similar
 molecules.

In another aspect, this invention relates to a composition which can be applied topically to the eye to lower intraocular pressure. This composition comprises one or more of the foregoing 15-acyl prostaglandins therein. The composition may comprise any of a variety of ophthalmically acceptable carriers as will be known to those skilled in the art of ocular drug delivery. A preferred method of application would be topically, in a pharmaceutically acceptable topical formulation. Such a carrier may be comprised of a saline and/or detergent, containing pharmaceutically required or advantageous adjuvants, along with an effective dose of the intraocular pressure reducing drug.

In accordance with a preferred embodiment of the present invention, the carrier comprises a solution having polysorbate 80 -10mM TRIS in the range of from about 0.05-1.0% by weight, and preferably about 0.1%, which is particularly suited for administration in the form of a liquid eye drop. This carrier may additionally comprise pharmaceutically advantageous adjuvants such as a preservative, antibiotic/antimycotic agents, pH buffers or osmotic balancers. In a preferred embodiment of the present invention, the intraocular pressure-reducing agent comprises a derivative of $\text{PGF}_{2\alpha}$, preferably one or a combination of the 15-isobutyryl, 15-valeryl, 15-isovaleryl or 15-pivaloyl $\text{PGF}_{2\alpha}$ derivatives.

The optimal concentration of the prostaglandin derivative is a function of a variety of factors, such as desired frequency of application and duration of effect, level of adverse side effects and considerations implicated by the chemical nature of the carrier. In general, however, concentrations are contemplated within the range of from about 0.0001% to 1%, preferably from 0.001% to 0.1% by weight in relation to the pharmaceutically acceptable carrier.

The esterification reactions for producing these 15-acyl compounds are illustrated in the Examples or are known to those skilled in the synthetic organic chemical arts.

The invention can be more fully understood by the following examples. All temperatures are in degrees centigrade.

EXAMPLE 1

Preparation of 15-Acetyl $\text{PGF}_{2\alpha}$

$\text{PGF}_{2\alpha}$ (50.1 mg, 0.14mmol) (Toray), n-butane boronic acid (28.8mg, 0.282mmol) and pyridine (2.0 ml) were combined. The reaction was stirred at 25° for 1.25 hours. Acetic anhydride (2 ml) was then added and the mixture was stirred continuously at 25° for 26 hours. The reaction mixture was cooled to 0° and quenched with water (3ml). The reaction mixture was then concentrated in vacuo at 30° to yield a yellow oil. The oil was redissolved in approximately 10 ml of ethyl acetate and washed with a 0.2M citrate buffer. The resulting aqueous layer was saturated with NaCl and extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate, concentrated in vacuo and chromatographed (HPLC, Whatman ODS-2 M-9, 60:40 $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ elution) to yield the title compound as a colorless oil.

$^1\text{H NMR}$ ppm (CDCl_3): δ 5.30-5.65 (m), 5.15(q), 4.45 (br), 4.20(br,s), 4.05(br,s), 1.45-2.30(m), 2.05(s), 1.30(br), 0.95(t).

$^{13}\text{C NMR}$ ppm (CDCl_3): δ 177.8, 170.8, 134.6, 130.1, 129.6, 129.1, 78.1, 74.9, 73.2, 55.8, 50.6, 42.7, 34.5, 33.0, 31.5, 26.4, 25.7, 24.9, 24.5, 22.5, 21.4, 14.0.

EXAMPLE 2

Preparation of 15-Isobutyryl $\text{PGF}_{2\alpha}$

$\text{PGF}_{2\alpha}$ (60.2mg, 0.17mmol) (Toray), n-butane boronic acid (26.3mg, 0.25mmol) and methylene chloride (0.5ml) were heated at reflux for 20 minutes before removal of the methylene chloride under a stream of dry nitrogen. The residue was dried in vacuo for 1.5 hours to remove water. This gave the intermediate 9,11-boronate derivative.

The resulting colorless boronate derivative was redissolved in methylene chloride (0.5ml), cooled to 0°

and treated with triethylamine (50.5mg, 0.6mmol), 4-dimethylaminopyridine (10mg) and isobutyric anhydride (85.4 mg, 0.54 mmol). The reaction mixture was warmed to 25° and stirred for 22 hours before being concentrated in vacuo redissolved in ethyl acetate and washed with a 0.2M citrate buffer. The ethyl acetate layer was dried over MgSO₄, concentrated in vacuo and chromatographed on HPLC to yield the title

compound as a colorless oil.
¹HNMR ppm (CDCl₃): δ 5.10-5.25 (m), 5.15 (q), 4.21 (t), 3.99 (t), 3.40-5.00 (br), 2.50 (m), 1.00-2.40 (m), 0.95 (t).

¹³CNMR ppm (CDCl₃): δ 177.9, 176.8, 134.3, 130.3, 129.6, 129.1, 78.2, 74.3, 73.3, 55.8, 50.6, 42.7, 34.5, 34.2, 33.1, 31.5, 26.4, 25.7, 24.8, 24.5, 22.5, 19.0, 18.9, 13.9.

Proceeding in a similar manner, but substituting for the isobutyric anhydride either valeryl chloride or isovaleryl chloride there was made the following two compounds:

15-valeryl PGF_{2α} - ¹HNMR (CDCl₃): δ 5.18-5.58(m), 5.15(q), 4.18(m), 3.98(m), 1.18-2.44(m), 0.91(t).

¹³CNMR (CDCl₃): δ 177.9, 173.6, 134.5, 130.3, 129.7, 129.2, 78.2, 74.6, 73.3, 55.9, 50.7, 42.7, 34.6, 34.5, 33.0, 31.5, 27.1, 26.4, 25.7, 24.9, 24.5, 22.6, 22.3, 14.0, 13.8.

15-isovaleryl PGF_{2α} - ¹HNMR (CDCl₃): δ 5.25-5.60(m), 5.15(m), 4.25(m), 4.18(m), 4.11(m), 3.98(m), 1.05(m)-2.45(m), 0.95(δ), 0.91(t).

¹³CNMR (CDCl₃): δ 177.9, 172.5, 134.5, 130.2, 129.6, 129.1, 78.2, 74.5, 73.3, 55.8, 50.6, 43.8, 42.7, 4.5, 33.0, 31.5, 26.4, 25.8, 24.9, 24.5, 22.5, 22.4, 13.9.

EXAMPLE 3

Preparation of 15-Pivaloyl PGF_{2α}

PGF_{2α} (40.4 mg, 0.114 mmol) was suspended in methylene chloride (1 ml) and cooled to 0° with an ice bath. A solution of diazomethane in ether was added dropwise to the above suspension until a yellow color persisted. The solution was warmed to 25° for 30 minutes before concentration in vacuo to yield the PGF_{2α} methyl ester as an oil. The crude ester was combined with n-butyl boronic acid (14 mg, 0.137 mmol) in methylene chloride (0.25 ml) and heated at reflux for 30 minutes. The reaction mixture was concentrated in vacuo and the residue dissolved in dry benzene. The benzene was evaporated under reduced pressure. The process was repeated twice to remove traces of water present from the reaction.

The crude PGF_{2α} 9.11-n-butyl boronate methyl ester thus prepared was dissolved in 0.2 ml of dry pyridine and treated with trimethylacetylchloride (42 μl, 0.34 mmol) and 4-dimethylaminopyridine (about 1 mg). The reaction mixture was stirred at 25° for 14 hours before being concentrated in vacuo. The residue was dissolved in ethyl acetate (10 ml) and washed with 10% aqueous citric acid (7 ml). The aqueous phase was extracted with ethyl acetate (3 x 7 ml) and the combined organic extract was washed with brine (7 ml), dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in methanol (3 ml) and stirred at 25° for 2 hours. The solvent was removed in vacuo and replaced with fresh methanol. This process was repeated once more. After removal of solvent, the residue was chromatographed (silica gel; 50-60% ethyl acetate-hexanes) to yield the 15-pivaloyl PGF_{2α} methyl ester as an oil.

15-pivaloyl PGF_{2α} methyl ester, (29.4 mg, 0.065 mmol) was dissolved in 0.33 ml of tetrahydrofuran and aqueous 0.5M lithium hydroxide solution (0.16 ml) was added dropwise at 0°. The two-phase mixture was stirred vigorously at 0° for 7 hours and at 25° for 1 hour. The mixture was cooled to 0° and acidified with 10% citric acid (7 ml). The reaction mixture was extracted with ethyl acetate (3 x 10ml) and the combined organic extract was washed with brine (7ml), dried over magnesium sulfate and concentrated in vacuo to yield the crude product. Flash chromatography on silica gel (6:4 ethyl acetate-hexanes with 0.5% acetic acid) yielded a colorless oil which was rechromatographed (6:4 ethyl acetate/hexanes) to yield purified 15-pivaloyl PGF_{2α}.

¹HNMR (300 MHz, CDCl₃): δ 5.3-5.6 (m, 4H); 5.17 (q, J=7Hz, 1H); 4.17 (br s, 1H); 2.34 (t, J= 7Hz, 2H); 2.0-2.4 (m, 7H), 1.2-1.9 (m-11H); 1.18 (s, 9H); 0.86 (distorted t, J = 7Hz, 2H);

¹³CNMR (75 MHz, CDCl₃): δ 178.9, 178.3, 134.2, 130.5, 129.8, 129.3, 78.2, 74.2, 73.3, 55.7, 50.5, 42.5, 38.7, 34.4, 32.9, 31.3, 26.9, 26.2, 26.2, 25.5, 24.6, 24.3, 22.3, 13.7.

EXAMPLE 4

Preparation of 15-acyl PGE₂

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Preparation of 15-acyl PGE₂ derivatives may be effected by the procedure described in Bundy, G. L., J. Am. Chem. Soc., 1972, 94, 2123.

PGA₂ (0.34 gm 1 mmol) is dissolved in pyridine (1 ml) and treated with acetic anhydride (1 ml). After
 10 24 hours at room temperature, the reaction mixture is quenched with water (0.5 ml), concentrated in vacuo
 and the residue chromatographed to yield 15-acetyl PGA₂. The 15-acetyl PGA₂ (0.282 g, 0.75 mmol) is
 then treated with 30% aqueous hydrogen peroxide (2 ml) and 1N aqueous sodium hydroxide (2 ml) in
 tetrahydrofuran (2 ml) for 8 hours to obtain 10,11-epoxy 15-acetyl PGA₂ after concentration in vacuo and
 chromatographic purification. Reduction of the 10,11-epoxy 15-acetyl PGA₂ (0.195 g, 0.5 mmol) with
 15 chromous acetate (0.376 g, 1 mmol) in acetic acid (2 ml) produces 15-acetyl PGE₂ along with 11- β -15-
 acetyl PGE₂ after chromatography. When acetic anhydride is replaced with another acid anhydride or acid
 chloride, the corresponding 15-acyl PGE₂ can be obtained.

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EXAMPLE 5Preparation of 15-acyl PGD₂

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PGD₂ (1 mmol, 0.35 g) is dissolved in CH₂Cl₂ (2ml) and treated with pyridine (3 mmol, 0.24 g) and
 acetic anhydride (1 mmol, 0.10 g). The reaction mixture is stirred at room temperature for 24 hours before
 being quenched with water. The organic layer is separated, dried over magnesium sulfate and concentrated
 30 in vacuo to yield a residue which is chromatographed to yield 15-acetyl PGD₂. When acetic anhydride is
 replaced with another acid anhydride or acid chloride, the corresponding 15-acyl PGD₂ can be obtained.

In accordance with minor variations on the procedures set forth in Examples 1-5 above, any of the 15-
 esters contemplated by this invention may be made.

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EXAMPLE 6

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Intraocular Pressure Reducing Effect in Rabbits

Starting with PGF_{2 α} , experimental quantities of the 5-acetyl, 15-isobutyryl, 15-valeryl, 15-isovaleryl and
 5-pivaloyl esters were prepared in accordance with the procedure Example 1 - 6. The resulting 15-acyl
 45 PGF_{2 α} compounds were added to a polysorbate carrier in amounts to produce a 0.01% and 0.1% solution
 of each ester. A group of 8 experimental rabbits was treated by administering one drop of each solution to
 the surface of the eye, and intraocular pressure was measured by applanation pneumatonometry (Model 30
 RT manufactured by Digilab) at the time of administration and at intervals of 3, 4, 6, 8 and 10 hours
 thereafter. The data of Table I were obtained:

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TABLE I

DECREASES IN INTRAOCULAR PRESSURE AT PREDETERMINED TIMES (HR) AFTER PROSTAGLANDIN ADMINISTRATION						
PG Dose %	Time (Hours)					
	0	3	4	6	8	10
PGF _{2α}						
0.01%	0	-2.3*	-1.3	-0.25	-	-
0.1%	0	-6.1**	-3.9**	-2.2**	-1.1	-
15-Acetyl PGF _{2α}						
0.01%	0	1.3	-0.7	-	-	-
0.1%	0	-3.3**	-3.3**	-	-	-
15-Valeryl PGF _{2α}						
0.01%	0	-2.4**	-2.3**	-2.0	-	-
0.1%	0	-0.25	-5.4**	-7.6**	-	-
15-Isobutyryl PGF _{2α}						
0.01%	0	-5.0**	-4.4**	-2.0*	-	-
0.1%	0	-2.75	-3.4	-6.6*	-5.6*	-4.7*
15-Isovaleryl PGF _{2α}						
0.01%	0	-4.0**	-5.1**	-5.2**	-	-
0.1%	0	-1.5	-5.1**	-7.5**	-5.2**	-3.2**
15-Pivaloyl PGF _{2α}						
0.01%	0	-	-3.4	-4.7**	-3.5	-1.6
0.1%	0	-	-0.25	-9.3**	-9.7**	-7.4**

* p<0.05.

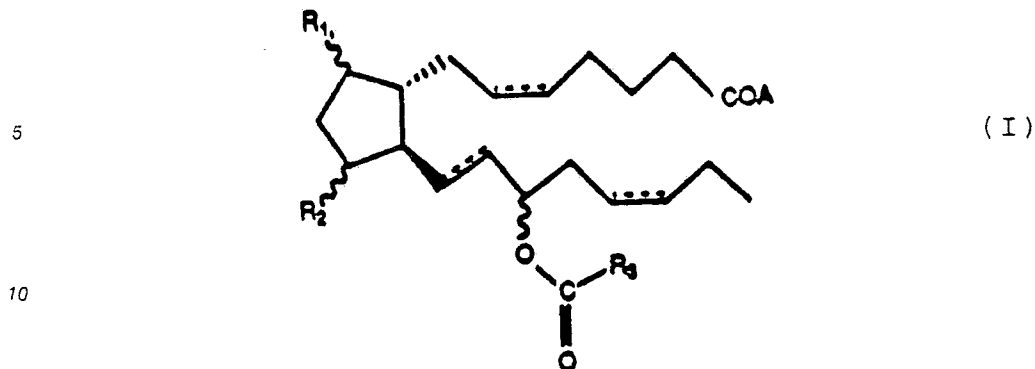
** p<0.01, n = 8

Comparison of the intraocular pressure-reducing effects of the foregoing series of 15-acyl PGF_{2α} esters with the parent compound reveals a marked increase in both the degree and duration of activity. Thus, with the 0.01% and 0.1% doses of the 15-isobutyryl, 15-valeryl, 15-isovaleryl and 15-pivaloyl esters, the magnitude of the decrease in intraocular pressure achieves a level that does not occur for either the 0.01% or 0.1% dose of PGF_{2α}. Moreover, the response to these 15-acyl PGF_{2α} derivatives appears more persistent than those recorded for PGF_{2α}. In addition, the 15-acyl derivatives produce less hyperemia than the parent compound.

Although this invention has been described in terms of certain preferred embodiments, other embodiments that are apparent to those of ordinary skill in the art are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

Claims

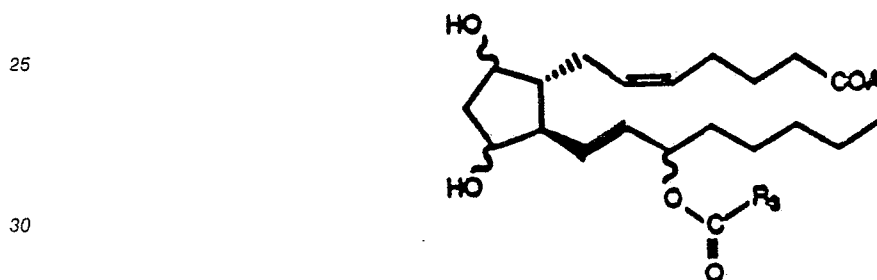
1. An ophthalmically acceptable composition or reducing ocular hypertension which comprises an ophthalmically acceptable excipient and at least one compound of the formula I:



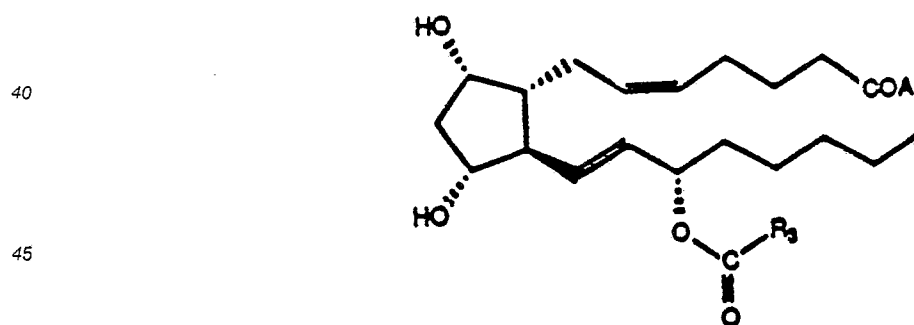
15 wherein the dotted lines represent a single bond, or a double bond in the cis or trans configuration: A is -OH or a pharmaceutically acceptable salt thereof or OR₅; R₁ and R₂ combined are -OH-OH, =O-OH, or -OH=O; R₃ is an acyclic hydrocarbon, saturated or unsaturated, having from 1 to 20 carbon atoms, or R₃ is -(CH₂)_nR₄ where n is 0-10; R₄ is an aliphatic ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R₅ is an aliphatic radical of from 1 to 10 carbon atoms.

20 2. The composition of claim 1 wherein R₁ and R₂ are both -OH groups.

3. The composition of claim 1 where the C-5 and C-13 bonds are cis and trans double bonds respectively, the compound having the following structure:

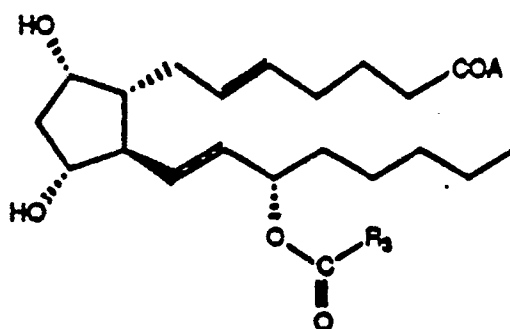


35 4. The composition of claim 1 where R₁, R₂ and the C-15 substituent are in the α-configuration, and the compound is of the following formula:

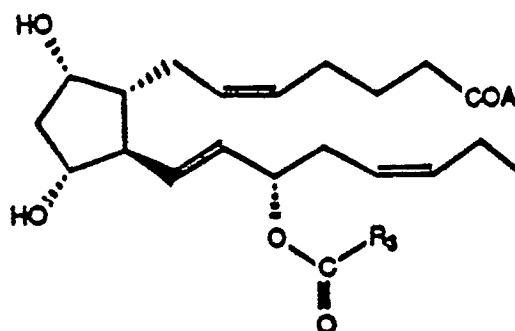


50 5. The composition of claim 1 which contains a 5-trans-PGF_{2α} compound having the following formula:

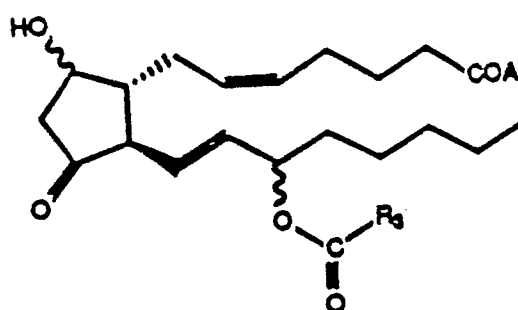
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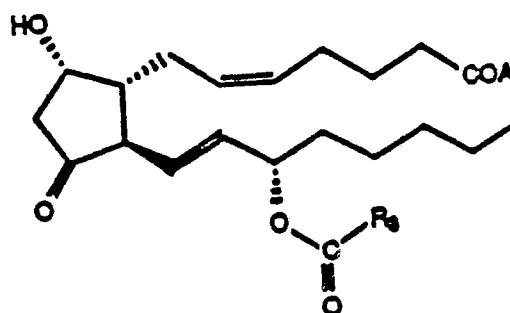
6. The composition of claim 1 where the compound is a $\text{PGF}_{3\alpha}$ of the following formula:



7. The composition of claim 1 wherein R_1 is $-\text{OH}$ and R_2 is $=\text{O}$ and the C-5 and C-13 bonds are respectively cis and trans, the compound having the following formula:



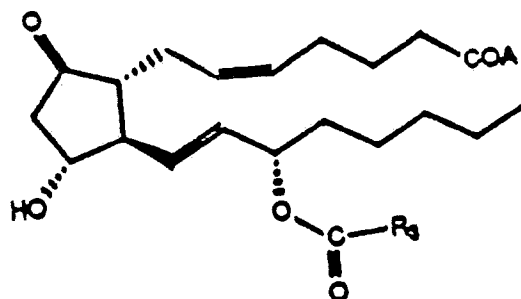
8. The composition of claim 7 where the R_1 group of that compound and the substituent at C-15 are in the α configuration, the PGD_2 compound having the following structure:



9. The composition of claim 1 wherein R_1 is $=\text{O}$ and R_2 is $-\text{OH}$ and the C-5 and C-13 bonds are respectively cis and trans, the PGE_2 compound having the following formula:

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10. The composition of any one of claims 2, 4, 5, 6 and 8 where R_3 is ethyl, propyl, butyl, or pentyl, or an isomer thereof.

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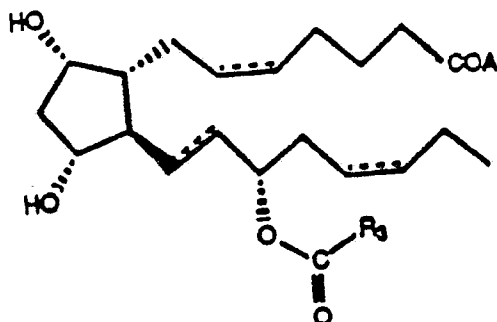
11. The composition of claim 4 or claim 5 where the R_3 group is $-\text{CH}(\text{CH}_3)_2$, $-(\text{CH}_2)_3\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$.

12. A composition as defined in any one of the preceding claims where the concentration of said compound or compounds contained in the composition is in the range of from about 0.0001% to 1% by weight in relation to the pharmaceutically acceptable excipient.

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13. A compound of formula (1a):

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(1a)

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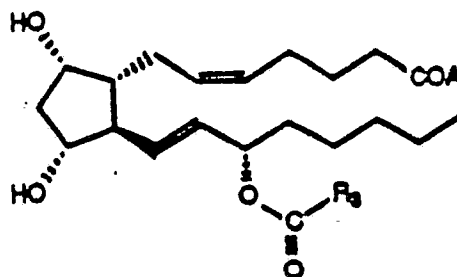
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wherein the dotted lines represent a single bond or a double bond in the cis or trans configuration; A is -OH or a pharmaceutically acceptable salt thereof or OR_5 ; R_3 is an acyclic hydrocarbon, saturated or unsaturated, having from 4 to 20 carbon atoms (eg. 5 or more carbon atoms), or R_3 is $-(\text{CH}_2)_n\text{R}_4$ where n is 0-10; R_4 is an aliphatic ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R_5 is an aliphatic radical of from 1 to 10 carbon atoms.

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14. The compound of claim 13 where the C-5 and C-13 bonds are cis and trans double bonds respectively, the compound having the following structure:

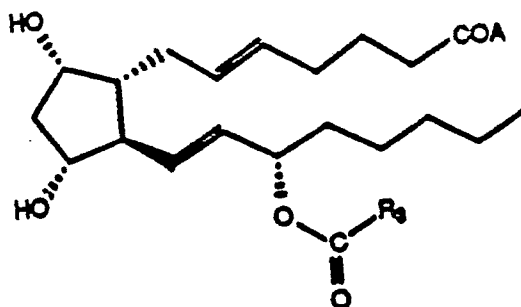
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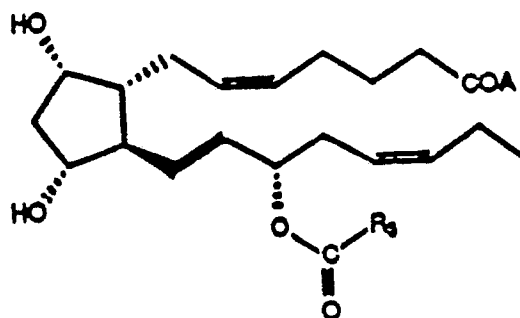
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15. The compound of claim 13 which is a 5-trans-PGF_{2α} of the following formula:

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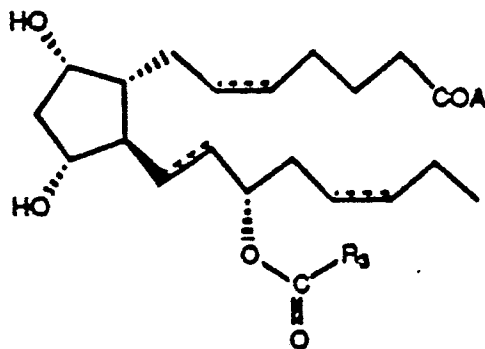


16. The compound of claim 13 where the compound is a $\text{PGF}_{3\alpha}$ of the following formula:



17. The compound of any one of claims 13 to 16 where R_3 is butyl or an isomeric form thereof.

18. A method for preparing a compound of the formula (1b) by esterifying the corresponding compound containing a 15-hydroxyl group, wherein said compound of the formula (1b) has the structure shown below:



(1b)

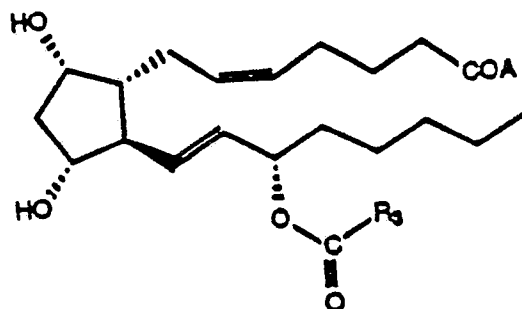
wherein the dashed bond represents a single bond or a double bond which can be in the cis or trans configuration; A is OH or $-\text{OR}_5$; R_3 is an acyclic hydrocarbon, saturated or unsaturated, having from 1 to 20 carbon atoms, or R_3 is $-(\text{CH}_2)_n\text{R}_4$ where n is 0-10; R_4 is a hydrocarbon ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R_5 is an aliphatic radical of from 1 to 10 carbon atoms; which method comprises:

- (a) esterifying the C-1 acid function;
- (b) treating the resulting C-1 ester with an alkyl-boronic acid in an inert solvent at a temperature up to reflux for up to 2 hours to effect formation of a 9,11-cyclic-boronate, C-1 ester;
- (c) treating the boronate compound, with or without a basic solvent with 4-dimethylaminopyridine and an acylating agent, eg. an acid anhydride or an acyl halide at ambient temperature or above for a time sufficient to effect esterification of the C-15 hydroxyl group;
- (d) hydrolyzing the 9,11-cyclic-boronate ester; and, when it is required to prepare a compound wherein R_5 is OH;
- (e) saponifying the C-1 ester.

19. The method of claim 18 where the compound of the formula (1b) has the following $\text{PGF}_{2\alpha}$ structure:

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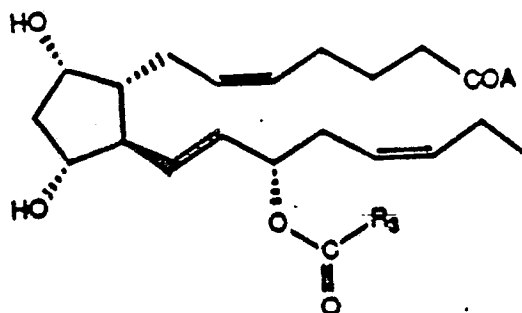
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or the following PGF_{3α} structure:

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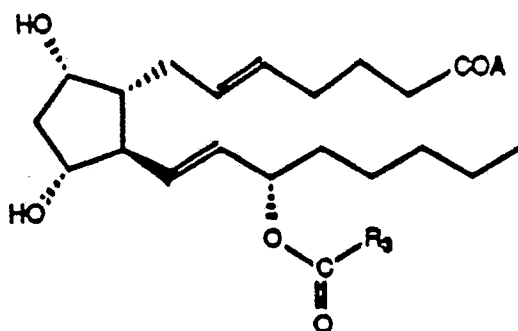


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or the following structure:

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and the acylating agent is, isobutyric anhydride, valeric anhydride, isovaleric anhydride, pivaloyl chloride or benzoic anhydride.

20. The use of a compound of the formula (1), (1a) or (1b), as defined in any of the preceding claims, for the manufacture of a medicament for treating ocular hypertension.

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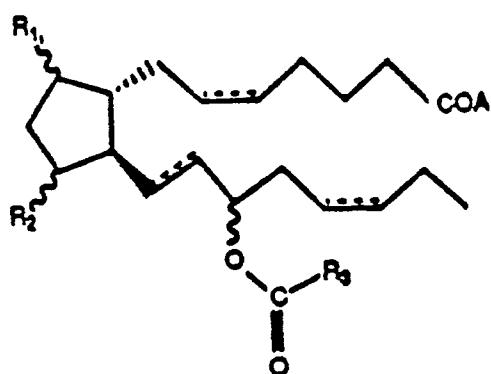
21. A compound of the formula (1a), as defined in any one of claims 13 to 17, for use in medicine, for example in treating ocular hypertension.

Claims for the following Contracting States: ES, GR

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1. A process for the preparation of an ophthalmically acceptable composition for reducing ocular hypertension containing an ophthalmically acceptable excipient and at least one compound of the formula (I):

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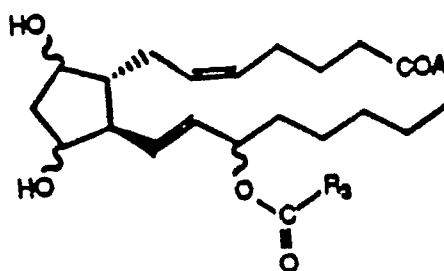


(I)

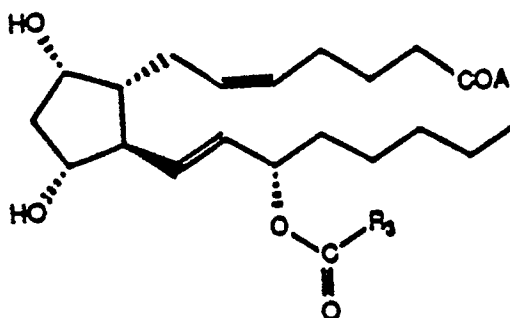
wherein the dotted lines represent a single bond, or a double bond in the cis or trans configuration: A is -OH or a pharmaceutically acceptable salt thereof or OR_5 ; R_1 and R_2 combined are -OH.-OH, =O.-OH, or -OH =O; R_3 is an acyclic hydrocarbon, saturated or unsaturated, having from 1 to 20 carbon atoms, or R_3 is $-(CH_2)_nR_4$ where n is 0-10; R_4 is an aliphatic ring from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R_5 is an aliphatic radical of from 1 to 10 carbon atoms; which process comprises bringing the compound into association with the ophthalmically acceptable excipient.

2. A process according to claim 1 wherein R_1 and R_2 are both -OH groups.

3. A process according to claim 1 where the C-5 and C-13 bonds are cis and trans double bonds respectively, the compound having the following structure:



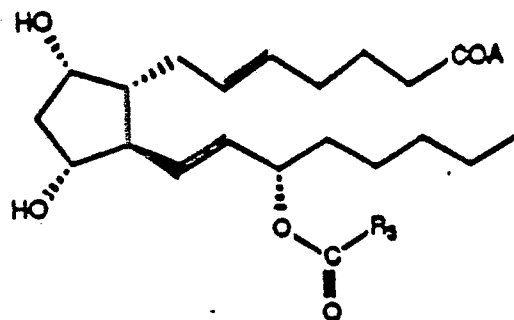
4. A process according to claim 1 where R_1 , R_2 and the C-15 substituent are in the α -configuration, and the compound is of the following formula:



5. A process according to claim 1 wherein the composition contains a 5-trans-PGF_{2α} compound having the following formula:

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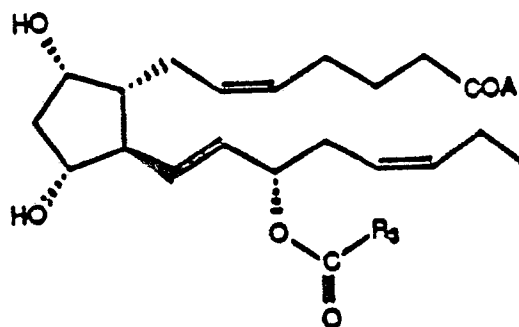


6. A process according to claim 1 where the compound is a PGF_{3α} of the following formula:

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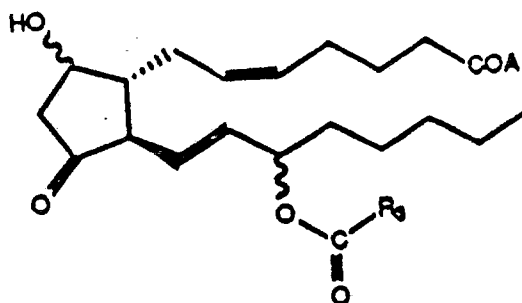


7. A process according to claim 1 wherein R₁ is -OH and R₂ is =O and the C-5 and C-13 bonds are respectively cis and trans, the compound having the following formula:

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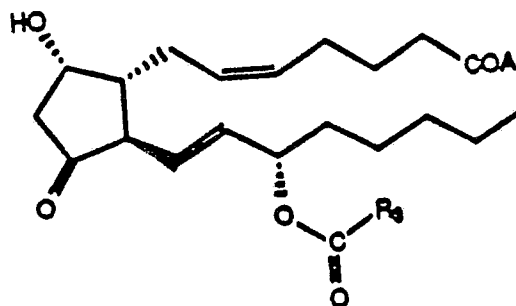


8. A process according to claim 7 wherein the R₁ group and the substituent at C-15 are in the α configuration, the PGD₂ compound having the following structure:

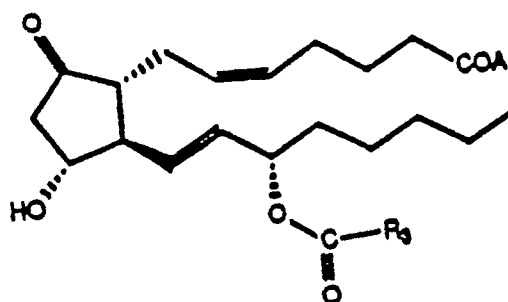
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9. A process according to claim 1 wherein R₁ is =O and R₂ is -OH and the C-5 and C-13 bonds are respectively cis and trans, the PGE₂ compound having the following formula:

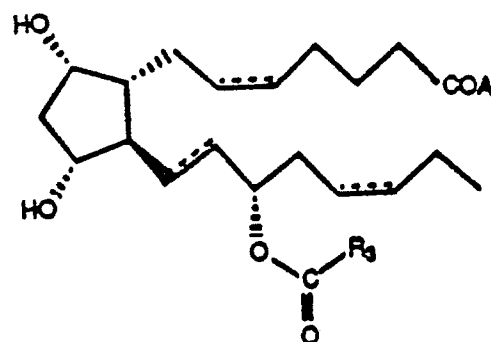


10. A process according to any one of claims 2, 4, 5, 6 and 8 where R_3 is ethyl, propyl, butyl, or pentyl, or an isomer thereof.

11. A process according to claim 4 or claim 5 where the R_3 group is $-\text{CH}(\text{CH}_3)_2$, $-(\text{CH}_2)_3\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, or $-\text{C}(\text{CH}_3)_3$.

12. A process according to any one of the preceding claims where the concentration of said compound or compounds contained in the composition is in the range of from about 0.0001% to 1% by weight in relation to the pharmaceutically acceptable excipient.

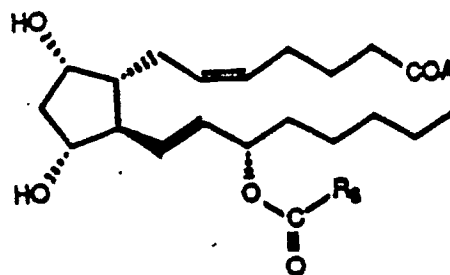
13. A process for the preparation of a compound of the formula (1a)



(1a)

wherein the dotted lines represent a single bond or a double bond in the cis or trans configuration; A is $-\text{OH}$ or a pharmaceutically acceptable salt thereof or OR_5 ; R_3 is an acyclic hydrocarbon, saturated or unsaturated, having from 4 to 20 carbon atoms (eg. 5 or more carbon atoms) or R_3 is $-(\text{CH}_2)_n\text{R}_4$ where n is 0-10; R_4 is an aliphatic ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R_5 is an aliphatic radical of from 1 to 10 carbon atoms; which process comprises esterifying the corresponding C-15 hydroxy compound, suitably protected where necessary, and thereafter deprotecting where necessary to give the compound of formula (1a).

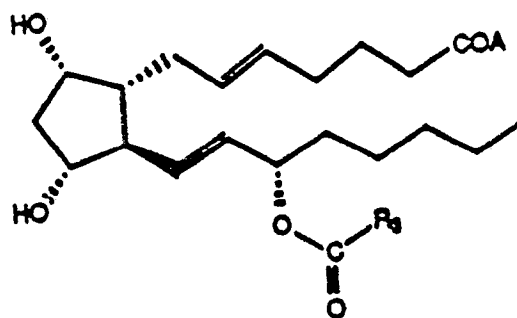
14. A method according to claim 13 wherein the C-5 and C-13 bonds in the compound of the formula (1a) are cis and trans double bonds respectively, the compound having the following structure:



15. A method according to claim 13 wherein the compound of the formula (1a) is a trans-PGF_{2α} of the following formula:

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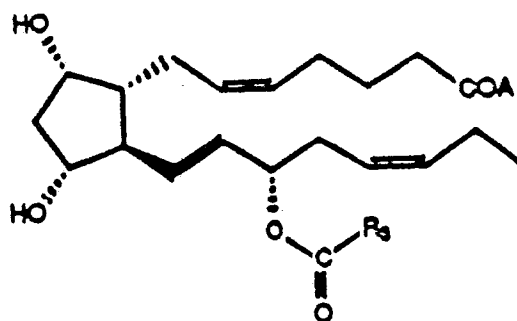


16. A method according to claim 13 wherein the compound of the formula (1a) is a $\text{PGF}_{3\alpha}$ of the following formula:

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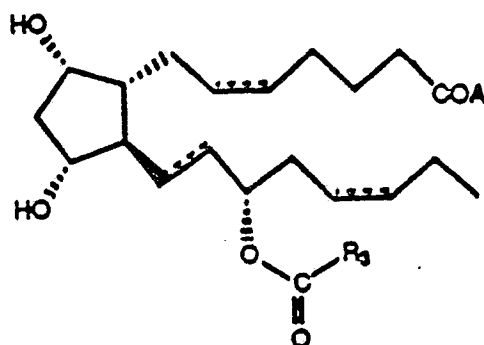


17. The method of any one of claims 13 to 16 where R_3 is butyl or an isomeric form thereof.

18. A method for preparing a compound of the formula (1b) by esterifying the corresponding compound containing a 15-hydroxyl group, wherein said compound of the formula (1b) has the structure shown below:

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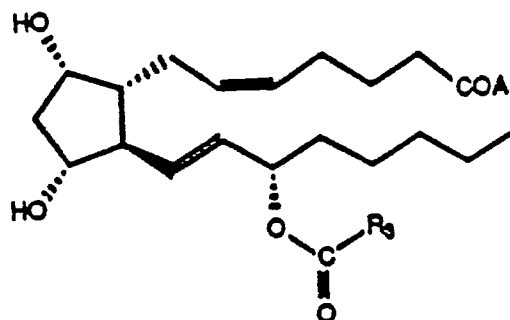


(1b)

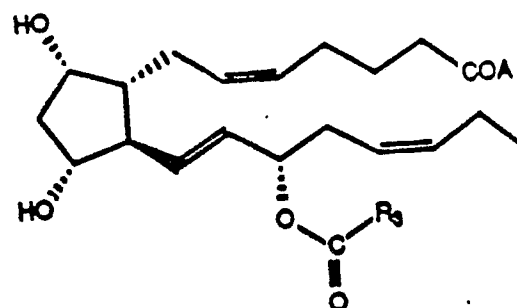
wherein the dashed bond represents a single bond or a double bond which can be in the cis or trans configuration; A is OH or $-\text{OR}_5$; R_3 is an acyclic hydrocarbon, saturated or unsaturated, having from 1 to 20 carbon atoms, or R_3 is $-(\text{CH}_2)_n\text{R}_4$ where n is 0-10; R_4 is a hydrocarbon ring of from 3 to 7 carbon atoms or an aromatic or heteroaromatic ring; and R_5 is an aliphatic radical of from 1 to 10 carbon atoms; which method comprises:

- (a) esterifying the C-1 acid function;
- (b) treating the resulting C-1 ester with an alkyl-boronic acid in an inert solvent at a temperature up to reflux for up to 2 hours to effect formation of a 9,11-cyclic-boronate, C-1 ester;
- (c) treating the boronate compound, with or without a basic solvent with 4-dimethylaminopyridine and an acylating agent, eg. an acid anhydride or an acyl halide at ambient temperature or above for a time sufficient to effect esterification of the C-15 hydroxyl group;
- (d) hydrolyzing the 9,11-cyclic-boronate esters; and when it is required to prepare a compound herein R_5 is OH;
- (e) saponifying the C-1 ester.

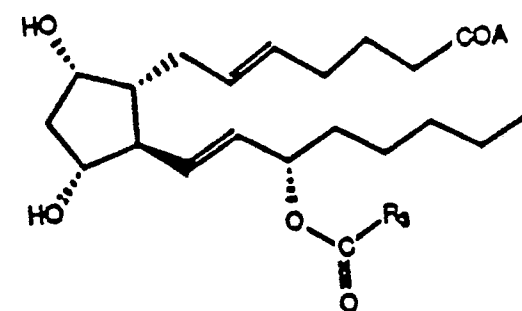
19. The method of claim 18 where the compound of the formula (1b) has the following PGF_{2α} structure:



or the following PGF_{3α} structure:



or the following structure



and the acylating agent is, isobutyric anhydride, valeric anhydride, isovaleric anhydride, pivaloyl chloride or benzoic anhydride.

20. The use of a compound of the formula (1), (1a) or (1b), as defined in any of the preceding claims, for the manufacture of a medicament for treating ocular hypertension.